review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Massachusetts Public Health Biologic Laboratories

No data have been provided by the manufacturer for tetanus antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell Inc.

No data have been provided by the manufacturer for tetanus antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Parke Davis & Company

No data have been provided by the manufacturer for this product for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Antitoxin Manufactured by Swiss Serum and Vaccine Institute Berne

No data have been provided by the manufacturer for tetanus antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

References

(1) BER VOLUME 2112.

(2) Bianchi, R., "Zur Serumprophylaxe des Tetanus," *Helvetica Medica Acta,* 29:2, 101–142, May 1962.

Tetanus Immune Globulin (Human) Manufactured by Abbott Laboratories

1. *Description.* This is a 16.5 percent ±1.5 percent solution of immunoglobulin prepared by cold alcohol fractionation of plasma from donors hyperimmunized with tetanus toxoid. The product is stabilized with 0.3 M glycine and contains 0.01 percent thimerosal as a preservative. Plasma samples employed are nonreactive for hepatitis associated antigen.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization of patients with tetanus-prone injuries, especially when there is doubt of adequate immunity or if there is a history of severe reactions to tetanus toxoid. It is also indicated in the treatment of tetanus. It may be administered simultaneously with tetanus toxoid. The recommended prophylactic dose is 250 units; therapeutic dose data are not adequate although it is stated that doses ranging from 500 units in infants to 56,000 units in adults have been employed.

In general the labeling is rather vague and could be greatly improved by incorporating the Public Health Service Advisory Committee on Immunization Practices recommendations (or their equivalent) regarding wound management. The desirability of simultaneous active immunization with adsorbed toxoid should be stressed.

b. *Contraindications.* Avoid intravenous injection. Hypersensitivity reactions are rare, as with other immune globulins.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data relative to this manufacturer's product are given. Indeed it appears that Abbott Laboratories has marketed this product only as a partially processed material (dry globulin powder) for further manufacture. There are apparently no data available. The manufacturer's submission to the Panel (Ref. 2) cites the general literature on the subject in support of efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data relative to this product are given. Indeed no data are available even from marketing experience since the final product for which the license was granted has never been sold. Over a 5-year period, a few hundred Kg of the globulin power has been sold to other manufacturers.

c. *Benefit/risk ratio.* A benefit-to-risk assessment for this product cannot be determined.

4. *Critique.* Since there are actually no data at all on the safety and efficacy of the actual product for which a license was granted, and the licensed product per se has not been sold, there is no basis for any judgment. Theoretically, the product could be put through final processing and sold at any time, and there is no reason to think that it would be any less safe or effective than other marketed products.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Tetanus Immune Globulin (Human) Manufactured by Armour Pharmaceutical Company

1. *Description.* Tetanus immune globulin (human), as manufactured by the Armour Pharmaceutical Company, is a sterile 10 percent to 18 percent solution of the immunoglobulin fraction prepared from plasma of persons who have been hyperimmunized with tetanus toxoid. The solution is made isotonic with glycine and contains up to 0.1 percent sodium chloride. The pH is adjusted with either sodium bicarbonate or acetic acid, and 0.01 percent thimerosal is added as preservative. It is packaged in 250 unit vials.

Human plasma is pooled and fractionated to freeze-dried Fraction II powder, using the alcohol fractionation method of Cohn. Fraction II is reconstituted in water, stabilizers and preservative are added, and the solution further processed to the final dosage forms. An extensive description of the process is made part of the submission.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be indicated as a prophylactic agent in persons whose injuries are liable to tetanus infection. Although experience

is limited, tetanus immune globulin (human) in large doses is stated as being possibly useful in the therapy of clinical tetanus.

b. *Contraindications.* None are specified. A precaution against intravenous administration is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data supporting the efficacy in humans of this product is cited in the submission to the Panel (Ref. 1), but no specific data relative to the Armour Pharmaceutical Company's product are provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data relative to the Armour Pharmaceutical Company's product are provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The information supplied by the manufacturer, the animal tests that this product is required to pass, and the general body of data regarding the safety and efficacy of tetanus immune globulin (human) is sufficient to place this product in Category I. The labeling should be more specific about indications for tetanus immune globulin prophylaxis in humans. The recommendations of the Public Health Service Advisory Committee on Immunization Practices are quite specific on this point, and could well be reproduced in their entirety in the labeling. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* This globulin is prepared from outdated blood or plasma donated to the Bureau of Laboratories, Michigan Department of Public Health, from American Red Cross Regional Blood Centers, and Michigan Blood Banks affiliated with the Blood Salvage Program of the Michigan Department of Public Health. Outdated plasma containing significant amounts of tetanus antitoxin, as demonstrated by the hemagglutination test, is pooled and fractionated by the cold alcohol fractionation procedures of Cohn. The final product is prepared as a 15 to 18 percent protein solution to which 2.25 percent glycine has been added as a stabilizer, and 1:10,000 thimerosal is added as a preservative. It is distributed in 250 unit vials.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for use in injured persons who need the immediate protection offered by tetanus antitoxin. Persons who have received the basic course of tetanus immunization are recommended to receive a booster dose of tetanus toxoid in preference to tetanus immune globulin. It is rather emphatically stated that the use of this material should be based on specific recommendations from full time health officers and/or the Division of Epidemiology of the Michigan Department of Public Health. For that reason the Public Health Service Advisory Committee on Immunization Practices recommendations are not reprinted as such.

A separate product, tetanus immune globulin (human) for therapeutic use, containing 2,000 units of tetanus antitoxin per bottle is also produced by this laboratory. The product under consideration therefore is for prophylactic use only and contains 250 units of tetanus antitoxin to be given intramuscularly.

b. *Contraindications.* None are listed. A precaution against intravenous administration is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are provided. It is noted that thousands of doses of Michigan Department of Public Health's tetanus immune globulin have been distributed in Michigan since 1965 with no reports of adverse reactions having been received. There is no evidence that this particular product has been responsible for the transmission of hepatitis B virus.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears satisfactory.

4. *Critique.* This submission (Ref. 3) is brief, but generally complete and adequate. Information provided by the manufacturer, the animal tests the product is required to pass, together with the general body of data concerning tetanus immune globulin (human) are sufficient to determine this product to be safe and effective. The recommendations for use and indications should be clarified in the labeling. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Cutter Laboratories, Inc.

1. *Description.* Tetanus immune globulin (human), Hyper-Tet®, is a solution of immunoglobulin prepared from venous blood of humans hyperimmunized with tetanus toxoid. Hyper-Tet® contains 16.5 percent ±1.5 percent protein dissolved in 0.3 M glycine and preserved with 1:10,000 thimerosal. The pH is adjusted with sodium carbonate.

Antibodies of homologous origin (as this product) have been shown to have a half life in the blood stream of 3.5 to 4.5 weeks.

Vials are said to contain 250 units of tetanus immune globulin, but the volume in which this is contained is not given.

The plasma is obtained exclusively by plasmapheresis (4 percent sodium citrate) and only donors of sufficient titers are selected.

Informed consent is obtained before a donor is enrolled in the program and the donor's health appears to be adequately monitored by annual examination.

Only plasma from individual donors that is tested at each donation for hepatitis B antigen and is negative when tested by any one of the official Bureau of Biologics' methods is used. Outdated preserved whole blood is used for fractionation into the components of plasma. According to the Bureau of Biologics' directions, a minimum of 10 donors should be used. The Cohn cold alcohol fractionation method is used. No preservatives are added during the pooling of the plasma or fractionation.

The final product solution is sterilized by filtration. Sodium chloride U.S.P. is added to a final concentration of 0.45 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is indicated in those patients who require immediate immunity against tetanus toxin, especially those who have little or no active immunity against it. It is also indicated in the regimen of treatment of active cases of tetanus.

In cases where the injury is severe and where the risk of potential tetanus infection is higher, a dose in excess of that recommended may be indicated. Dosage: for adults, 250 units should be given by deep intramuscular injection. In small children the dose may be calculated by the body weight (4.0 units per kg) or it may be advisable to administer the entire contents of the vial. The Public Health Service Advisory

Committee on Immunization Practices is cited as a guide in would management.

b. *Contraindications.* This product is contraindicated in individuals who are known to have had an allergic response to immunoglobulin.

It is warned that the product should not be given intravenously, since such injections, on occasion, cause a precipitous fall in blood pressure, and a picture not unlike anaphylaxis. Skin tests should not be carried out because the product is known to cause a localized area of inflammation which can be misinterpreted as a positive allergic reaction.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several clinical studies consisting of measurement of antibody increase are reported in the submission to the Panel (Ref. 4) for this product. Twenty subjects were given 400 units of Hyper-Tet® and antibody levels compared with 15 subjects receiving 1,500 units of equine antitoxin. At first, serum levels were higher for those receiving the equine product in the high dosage, but after about 6 weeks higher levels of antitoxin remained among those receiving the human immunoglobulin.

Studies were also carried out measuring the response when subjects were given immunoglobulin alone or in combination with tetanus toxoid. Satisfactory (0.1) antitoxin levels were achieved with or without simultaneous administration of toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* References to safety reported in the literature are cited in the submission. The product is tested by several chemical tests as to content of protein, chloride, glycine, and for stability and pH, and electrophoretic identity.

c. *Benefit/risk ratio.* Although no human efficacy studies are available, on theoretical grounds the benefit-to-risk assessment should be satisfactory .

4. *Critique.* Labeling is satisfactory, although it may be desirable to give the approximate volume of plasma necessary to provide the recommended dose of 250 units. No data from the manufacturer's complaint files were provided. It is unclear how many donors are utilized for pooling of sera. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Dow Chemical Company

1. *Description.* Tetanus immune globulin (human), as produced by the Dow Chemical Company, is a sterile solution of immunoglobulin obtained from the pooled venous blood of humans hyperimmunized with tetanus toxiod. The contents of the vial or syringe are standardized to contain 250 units of tetanus antitoxin. It is prepared by Cohn cold alcohol fractionation, stabilized with 2.25 percent glycine, and preserved with 1:10,000 thimerosal.

2. *Labeling*—a. *Recommended use/ indications.* This product is said to be indicated for passive immunization of persons incurring wounds other than clean, minor wounds only when the history of tetanus toxoid administration is uncertain, or if only one or no toxoid injection has been administered; or if the wound has been unattended for more than 24 hours even with the history of two toxoid injections.

b. *Contraindications.* None are listed. A precaution against intravenous use is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of literature supporting the efficacy of human tetanus immune globulin is cited in the submission (Ref. 5), but no specific data relative to the Dow Chemical Company's product are provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Ten human volunteers were given 250 units of tetanus immune globulin (human) intramuscularly, and observed immediately after the injection, and once daily at 24, 48, and 72 hours. No unusual untoward reactions were noted in these 10 volunteers. The general body of data supporting the human safety of tetanus immune globulin (human) is cited as well.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This submission is supported by a large number of reprints of data supporting the safety and efficacy of human tetanus immune globulin. Although little of the data applies directly to the Dow Chemical Company's product, the animal safety and efficacy tests, together with the general body of data supporting the safety and efficacy of human tetanus immune globulin, is sufficient to place this product in Category I. (See Generic Statement.)

In the labeling, the recommendations for use should be clarified.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by E.R. Squibb & Sons, Inc.

1. *Description.* This is a 16.5 percent solution of Cohn Fraction II obtained from plasma of selected donors immunized with tetanus toxoid. It is stabilized with 0.3 M glycine and contains 0.01 percent thimerosal as preservative.

2. *Labeling*—a. *Recommended use/ indications.* This product is intended for passive immunization against tetanus. It is recommended for prophylactic use (250 units) in patients lacking a recent (5 year) history of active immunization or in those never immunized or of uncertain status. Therapeutic doses of 3,000 units or more (up to 6,000 units) are recommended as part of the treatment of clinical tetanus. The narrative of the package insert is fairly adequate, but would be improved from the user's point-of-view by including the Public Health Service Advisory Committee on Immunization Practices wound management recommendations in tabular form. Also, the advisability of adsorbed tetanus toxoid for simultaneous active immunization needs to be stressed.

b. *Contraindications.* Essentially none, except avoidance of intravenous injections. Hypersensitivity reactions are rare.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on this product are given. The submission to the Panel (Ref. 6) refers to the American College of Surgeons 1972 recommendations and to a review by Heurich (Ref. 7) for prophylactic use of tetanus immune globulin and other aspects of management of tetanus.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data, not even the approximate number of doses distributed, are provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product cannot be determined.

4. *Critique.* The manufacturer has supplied no information on human safety and efficacy for this specific product. The product does not appear to

have been produced for a number of years.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked because this product has not been marketed for a number of years and there are insufficient data on labeling, safety, and effectiveness.

Tetanus Immune Globulin (Human) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This is a 10 to 18 percent solution of globulin derived from plasma of donors hyperimmunized with tetanus toxoid. The globulin is prepared by a modified Cohn alcohol fractionation process and is dissolved in 0.3 M glycine containing not more than 0.25 percent sodium chloride. The preservative is thimerosal, 0.01 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization against tetanus. For prophylactic use, a dose of 250 units is recommended in injured individuals who have not been previously immunized with tetanus toxoid or for those with vague histories or with lapses of many years since the last booster. Prophylactic use is also recommended when the risk is great from extensive contaminated wounds. Simultaneous active immunization is also recommended. For treatment purposes in the management of clinical tetanus, it is noted that experience is limited and that doses of 3,000 to 6,000 units have been used with mixed results. The instructions given are rather vague and could be improved by incorporation of the Public Health Service Advisory Committee on Immunization Practices recommendations on wound management with appropriate updating of the literature references. They should also specify adsorbed toxoid for use in simultaneous active immunization.

b. *Contraindications.* Essentially those for immunoglobulin, especially avoiding intravenous injection. Hypersensitivity reactions are extremely rare.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims for efficacy are based on the identity of the product and are supported by a review in the submission (Ref. 8) of a number of literature citations relevant to the use of tetanus immune globulin in general. No specific data on this particular product are given.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No significant reactions were reported for 1970 to 1974. A few hundred thousand doses were distributed over a 5-year period. Some mild local inflammatory reactions for immunoglobulin given for measles were seen in 1.2 percent of cases in 1969. In general, immune globulin is a product of proven safety which rarely presents a serious problem. There is no serious question of safety for this product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

4. *Critique.* There are no efficacy data in humans for this specific product. Tetanus immune globulin in a generic sense is an accepted product for the prophylaxis of tetanus where indicated. Its use along with other appropriate treatment is clearly accepted in cases of clinical tetanus although the appropriate dosage for this purpose is not clearly established. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is a 16.5 percent (±1.5 percent) solution of globulin prepared by cold ethanol fractionation of human plasma selected by hemagglutination tests to contain significant levels of tetanus antitoxin. It is stabilized by 0.3 M glycine and contains 0.01 percent thimerosal as a preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is intended for passive immunization in persons at risk of tetanus who lack a reliable history of active immunization. It is stated that a booster response to tetanus toxoid (even after 20 years) is preferred to tetanus antitoxin. Doses of 250 units given intramuscularly are recommended for prophylaxis. Simultaneous active immunization with adsorbed toxoid is always recommended. No specific recommendations on therapeutic use are given; in this case the use is advised to contact the producer. In general, the labeling is brief and to the point, although it is less easy to follow than the Public Health Service Advisory Committee on Immunization Practices guidelines.

b. *Contraindications.* Essentially none. Avoid intravenous injection. Hypersensitivity reactions are rare.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Publications from the manufacturer's laboratory relative to the use of the product are cited in the submission (Ref. 9). These pioneering and often cited papers document the recommended use of the 250 unit dose for prophylaxis as judged by maintenance of protective antitoxin levels. These studies document the feasibility and desirability of combined active-passive immunization, showing the superiority of adsorbed toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* From the years 1969 to 1973, thousands of 250 unit vials were distributed without incident. Considering the proven safety of immune globulin in general, there is no question of safety.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

4. *Critique.* This is a brief, but well-documented report from a laboratory that helped pioneer the concept of tetanus immune globulin. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This product is a solution of human immunoglobulin prepared by Cohn cold ethanol fractionation of plasma drawn from donors who have been hyperimmunized with tetanus toxoid. The solution is dissolved in 0.3 molar glycine and contains thimerosal 1:10,000 added as preservative. The protein content is given as 10 to 18 percent globulin and the antibody content is given as at least 250 units of tetanus antitoxin per dose.

The general procedure for immunization of donors is said to conform to the Federal regulations for source plasma, human.

2. *Labeling*—a. *Recommended use/indications.* This product is indicated in injured persons not actively immunized or in whom the immunization status is undetermined and who otherwise would be candidates for an injection of tetanus antitoxin for protection against the possibility of the development of tetanus. Passive protection need be considered only when the patient has had fewer than two previous injections of tetanus toxoid or when the wound has been untended for more than 24 hours.

The usual dosage for adults and children is 250 units (entire contents of one single-dose prefilled disposable syringe) regardless of body weight. The same dose is indicated for adults and children because theoretically the same amount of toxin will be produced in both.

More than 250 units may be indicated, together with antibiotics, when the risk of potential infection is great.

The advantages of using tetanus immune globulin rather than equine or bovine antitoxin are outlined. The product is also recommended for treatment of tetanus, but the dosage may vary, and it is said that 3,000 to 6,000 units have been used.

b. *Contraindications.* None are specifically given, but it is pointed out that the material should not be given intravenously, that local tenderness and stiffness of the muscles may occur after injection. Hypersensitivity to injections of immune serum globulin is mentioned as a possibility and in highly allergic individuals repeated injections may lead to anaphylactic shock or even death.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Pertinent human studies are cited in the submission (Ref. 10) but no serologic studies of the manufacturer's product appear to have been carried out.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No special testing of the manufacturer's product appears to have been carried out. However, between 1969 and 1974 a sizable number of doses have been distributed without any reports of adverse reactions having been received.

c. *Benefit/risk ratio.* Assuming this product is effective as discussed in the Generic Statement, the benefit-to-risk assessment should be satisfactory.

4. *Critique.* This is a rather brief application, which provides no specific data on the efficacy of the manufacturer's own product. The approximate volume containing one dose is not given. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Metabolic, Inc.

No data have been provided by the manufacturer for tetanus immune globulin, for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Tetanus Immune Globulin (Human) Manufactured by Osterreichisches Institut fur Haemoderivate G.M.B.H.

1. *Description.* This is a tetanus immune globulin of human origin containing, per mL, 250 U.S. units of tetanus antitoxin, 100 to 160 mg of total protein, 22.5 mg glycine, 3.0 mg sodium chloride, and 1:10,000 thimerosal as preservative. The product is said to be prepared from blood of healthy donors who had been immunized against tetanus. A good description of the production process is provided, which basically consists of passage of a plasma pool through an adsorption column, followed by cold ethanol fractionation. The final protein concentration varies between 10 percent and 16 percent w/v.

2. *Labeling*—a. *Recommended use/indications.* This product is said to be indicated in case of injury with risk of tetanus infection in instances in which adequate active immunity is not proven. "Adequate" active immunity is nowhere defined. Simultaneous active-passive vaccination is said to be indicated in cases of (1) lacking or inadequate active immunization or if definite history of immunization cannot be ascertained, (2) risk of antibody deficiency syndrome or reduced capacity of antibody formation, (3) risk of heavy contamination of the wound with tetanus bacilli, (4) injuries dating back longer than 3 days, and (5) serious burns.

b. *Contraindications.* The only contraindication listed is a previous severe reaction following the administration of tetanus immune globulin (human). A precaution against intravenous administration is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are provided. The submission (Ref. 11) contains an interesting report of one prophylactic failure in one case of a femur heavily injured by a slaughtering apparatus. The patient received active and passive immunization on the same day, but developed severe tetanus a few days later and died. The immunization history of this patient would have been considerable interest.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Radioimmunoassays for the determination of hepatitis B antigen are carried out on both the raw source plasma and the final product. The submission notes that no adverse reactions have been reported, and there have been no reports of transmission of hepatitis with this product. No prospective clinical data are presented, however.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The information provided by the manufacturer, the animal tests that this product is required to pass, and the general body of knowledge concerning the safety and efficacy of human tetanus immune globulin are sufficient to place this product in Category I for prophylactic use.

No labeling was provided in the sense of a package insert. Pages 3 through 9 of the submission appear to serve the same purpose, and suffer significantly in the translation from German to English. Extensive revision will be necessary to put the language into contemporary usage. "Adequate" active immunization must be defined, and reference should be made to official recommendations of advisory bodies such as the Public Health Service Advisory Committee on Immunization Practices. (See Generic Statement.)

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Immune Globulin (Human) Manufactured by Parke, Davis & Co.

1. *Description.* This product is a concentrated solution of tetanus antitoxin as immunoglobulin prepared from the blood of adults who have been hyperimmunized with tetanus toxoid. It is prepared from plasma, which was nonreactive when tested for hepatitis B antigen. The globulin is precipitated by the Cohn cold ethanol fractionation process and supplied as a sterile standardized solution containing 100 to 180 mg of protein per mL (10 to 18 percent). The globulin fraction is dissolved in a 2.25 percent solution of aminoacetic acid (glycine) containing approximately 0.2 percent sodium chloride. It is preserved with 0.01 percent thimerosal and adjusted to approximately pH 6.8 with sodium acetate buffer.

2. *Labeling*—a. *Recommended use/indications.* This product is